

(54) procedure for the production of adsorbent polymers for the Haemoperfusion

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Patent claim:

Procedure for the production of highly porous adsorbent polymers on the basis, applicable to the Haemoperfusion, of interlaced aromatic polymers, characterized by the fact that technical chlormethylgruppenhaltige solvent-free Divinylbenzen interlaced Polystyrene in presence of pouring inert funds, chlorinated hydrocarbons and Friedel Crafts catalysts is preferably after-interlaced and afterwards from the inert fund exempted, whereby the Vernetzeranteil, related to Divinylbenzen, consists of 2 to 8 mA % and the substitution degrees at groups of chlorine methyls more largely 0.4 and will preserve products the surfaces more largely 800m²/g and more largely 300m²/ml water-damp adsorbent polymers to possess, whose possible, still existing groups of remainder chlorine methyls are if necessary alkalinely soaped or veraethert with Polyolen and/or polyethylene glycols, and before the use in the Haemoperfusion to be cleaned, coated and sterilized.

Area of application of the invention

With the treatment of patients with loss of function or function restriction of the kidneys, for acute intoxication, loss of function of the liver including hepatorenalen Syndroms it is possible, the blood of pollutants, like poisons and urine-requiring substances to exempt. This task is solvable by use of adsorbent polymers by means of Haemoperfusion.

Characteristics of the well-known technical solutions

of adsorbent polymers are manufactured generally by suspension polymerization by monomers with a cross

linkage material in presence of inert materials. The inert materials are removed for polymers after the polymerization again from that and are responsible in the association with the Vernetzer for the degree of porosity. As usable inert funds are for example referred to aliphatic and aromatic hydrocarbons, alcohols, ester, Ketone and soluble polymers. According to this principle porosity is controllable, however surface values and adsorptivities of certain activated carbon cannot be achieved (J.Seidl, chem. one prumysl 25 [50], 416-419). Further synthesis principles describe different ways in order to come to still more porous Adsorbentien with improved adsorptive properties. The principle of the Nachvernetzung of polymers is revealed here as solution method. In US-HP of 4.191.813 subsequent cross-linking is described by low interlaced Vinylbenzylchloridkopolymeren in presence of pouring Inermitteln by Friedel Crafts catalysts.

US-HP of 4.263.407 states the way of over small interlaced makroretikulare aromatic polymers by Nachvernetzung. For this that polymers in an inert source fund, which the Vernetzer in the form of polyfunctional alkylating -, acylation or sulfur halides contains, one pours and in presence of Friedel Crafts catalysts one after-interlaces. Davankov (Angew. macromolecular chemistry 91 [1980], 127-142, dd-HP of 85,644) and dd-HP of 125,824 describe the same "principle at the Polystyren and/or to Styren Divinylbenzen styren-Divinylbenzen-Kopolymeren to 1 mol % cross-linking. Beside polyfunctional alkylating and acylation funds Monochloridmethylether are assigned. Quoted procedures possess disadvantages, which of it consist that with the synthesis of adsorbent polymers by means of Nachvernetzung partially technically with difficulty accessible basic materials, as the assigned Vinylbenzylchlorid, which must be assigned polyfunctional Vernetzer or polymers, which contain Divinylbenzenvernetzung to 1 mol %. For the Haemoperfusion so far adsorbent polymers are used, which are manufactured in procedures of the kopolymerisation by cross linkage materials in high concentrations in presence of inert funds. As is still shown, these products are clearly underlaid for those of the procedure according to invention in the adsorptivities.

A goal of the invention

The goal of the invention is as simple a procedure for the production of Adsorbentien with high surface and improved adsorbates as possible characteristics with the Haemoperfusion.

Statement of the nature of the invention

the task of the invention consisted of developing on the basis of technical pre and intermediate products a procedure which

corresponds to the goal of the invention.

It was now found that one can manufacture Adsorbentien with surface large according to ($> 800 \text{ m}^2/\text{g}$) and improved adsorbates characteristics for medicines, blood poisons and urine-requiring substances, if one na.chvernetzt technical chlormethylgruppenhaltige polymers, preferably Styren Divinylbenzen styren-Divinylbenzen-Kopolymere in presence of pouring Inermitteln, whereby the cross-linking degree of 2 to 8 mA %an Divinylbenzen consists of and the substitution degree at groups of chlorine methyls more largely 0.4 (11.5% Cl), preferably 0.7 (17.8% CD is.

The procedures of the syntheses that output polymers and the procedures of the introduction of groups of chlorine methyls are well-known. With the aromatic polymers, which serve as basis for the adsorbents, it concerns products, which are manufactured by perlpolymerisation of a mixture from one or more Monovinylverbindungen, one or several Polyvinylverbindungen with or without additive of one or several kopolymerisierbarer polar Vinylverbindungen and with or without additive of inert materials. As usable Monovinylverbindungen are for example referred to: Styren, substituted Styrene and Vinylnaphthalin.

Preferential Polyvinylverbindungen is DivinylbenzeneundTrivinylbenzene. Technical meaning predominantly interlaced Styrene attained e.g. on the basis of Styren and Divinylbenzen if necessary under additive further polar Monomerer, like acrylic acid esters and acrylonitrile and/or faellenden and/or pouring.inert funds e.g. aliphatic or aromatic hydrocarbons. For the achievement of optimum adsorbent-polymere from kopolymeren one proceeds, which according to invention possesses a Divinylbenzengehalt of 2 bis8Ma. %. The introduction of groups of chlorine methyls to such polymers is possible in well-known way with Chlormethylierungsmitteln such as Monochlordimethylether, Dichlordimethylether, mixtures from formaldehyde and/or formaldehyde supplying substances and hydrogen chloride and/or with further additive of methanol and a chlorine donor such as SOCl_2 , ClSO_3H and $\text{SC}^{\wedge}\text{C}^{\wedge}$. Mixtures from Methylal and a chlorine donor are likewise applicable.

A polymere substituted after such a Chlormethylierungsverfahren after distance of surplus Chlormethylierungsmittel by washing with a suitable solvent, methanol is preferably aminiert, also industrially for the production of anion exchangers with a suitable amine, suitable for the technical use. If one converts such methanol-damp Chlormethylat to the Nachvernetzung in presence of a Friedel Crafts catalyst and in presence of an inert fund, e.g. Dichlorethan, at increased temperature, then one preserves after-interlaced polymers, which correspond not to the demands however regarding its porosity and surface to a polymer adsorbent to the use in the Haemoperfusion. Preserved after-interlaced polymers exhibit surfaces between $50\text{-}600 \text{ m}^2/\text{g}$. A technical Chlormethylat can be transferred

however to surprising way then according to invention in a highly effective adsorbent by Nachvernetzung, if before the addition of the Friedel Crafts catalyst and before the necessary rise in temperature a distance of the solvent used as detergents of the technical Chlormethylates is e.g. affected, methanol on values $< 5 \text{ mA } \%$, as the solvent is removed either by drying process or by displacement with a chlorinated hydrocarbon, preferably Dichlorethan oder Tetrachloraethan.

That, as described above, to a large extent solvent-free chlormethylgruppenhaltige output polymers becomes, if necessary, in a further quantity of a halogenhaltigen hydrocarbon, e.g. Dichlorethan or Tetrachloraethan, poured, a Friedel Crafts Katalysator wie iron three-chloride, tin tetrachloride or aluminum tri chloride added and the Nachvernetzung during simultaneous porosity constitution at temperatures more largely 75°C caused.

The swelling chlormethylgruppenhaltigen polymers in inert chlorinated hydrocarbon is generally sufficient after 1 to 4 hours at room temperature, whereby the kind of the inert fund and the circumstance polymers to the inert fund of crucial effect on porosity and thus on the final product characteristics are. In the procedure according to invention as inert funds Dichlorethan and Tetrachloraethan particularly worked. Other inert funds are not impossible however. The circumstance polymere to inert fund can be varied by the deficiency swelling, straight still agitatable, up to the surplus swelling with very good agitating ability. The swelling capability depends on the Chlormethylierungsgrad and output cross-linking.

The catalyst concentration can be varied within far borders and affected likewise the final product characteristics. So an incomplete Nachvernetzung has a negative effect on the porosity constitution.

The catalyst portion on at least $20 \text{ mA } \%$ is according to invention to select related to polymere, and the Chlormethylierungsgrad at least 0.4, preferably however 0.7. The reaction temperature and response times are likewise of effect and the final product characteristics, whereby temperatures between 75 to 120°C und response times from 2 to 20h are favorable reaction parameters. A gradual heating from ever 30 to 60 minutes over 40, 50, 60, 70 and 80°C proved for the structure constitution as favourable. After deal of the reaction the product must be exempted and hydrophiliert from the chlorinated hydrocarbon. In addition a washing with methanol particularly worked.

The synthesis that adsorbent polymers in the procedure according to invention offers the following benefits: against the state of the art, with which technically with difficulty accessible basic materials e.g. bifunctional connections to

the Nachvernetzung and low interlaced output polymers are assigned, which lead with the Nachvernetzung to Adsorbentien with not optimum adsorptivities for each unit volume, now technically well accessible chlormethylierte polymers begun, which improved adsorptivities, related to the unit volume, to supply. Thus only about a third of the Friedel Crafts catalyst in relation to the conditions are needed. By the smaller swelling that output polymers is further an inert fund saving up to approximately 50% possible.

According to invention manufactured the adsorbent polymers exhibit substantially higher surfaces and thus adsorptivities, than the comparable commercial products. The medicine adsorption could opposite conventional, for which Haemoperfusion assigned adsorbent polymers to around approximately 60% are increased. The products are characterised by a good Hydrophilie and are wettable after drying or wash trials well and directly with water again.

For the improvement of the blood compatibility it is possible to soap or etherify with Polyolen and/or polyethylene glycols still existing groups of chlorine methyls alkalinely.

Before the use to the Haemoperfusion the adsorbent polymers are conditioned. For this are characterized a further cleaning step, by wash trials by organic solvents such as Tetra, acetone, methanol, Toluol and water, as well as a coating step with e.g. Poly (2 hydroxyethylenmethacrylat), celluloseacetat, collodion or albumin necessary for the better blood compatibility and a sterilization step.

Example 1:

In a Sulfierkolben, equipped with thermometer, rueckflusskuehler and 100g chlormethylierten 3.5% interlaced Styren Divinylbenzen styren-Divinylbenzen-Kopolymeren with a chlorine value of 19,3% with 275g Dichlorethan transferred, 2h at ambient temperature poured and after it with 65g aluminum tri chloride shifts. Afterwards one with 40, 50, 60 and 70°C and 20 h each are agitated with 83-85°C. The mixture is hydrolyzed with water, washed with methanol and again with water.

The product possesses the following characteristic values:

Surface: 1,080 m²/g
Water content: 48,5 %

Surface for each unit
volume of damp adsorbents: 312m²/ml

example 2:

Similar to example 1 100g same chlormethylierten 3.5% interlaced Styren Divinylbenzen styren-Divinylbenzen-Kopolymeren with 320g of the Tetrachloraethan are shifted, 4h at ambient temperature pour and after it with 15ml tin tetrachloride are shifted and one hour each with 60,70, 80,90°C and further 10h with 105°C agitated. The product cooled off is separated and washed with methanol, methanol water 50:50 and water. The product exhibits the following characteristic values:

Surface: 1155m²/g

water content: 41,2%

Surface for each unit volume of damp adsorbents:
460m²/ml.

Example 3:

In a Sulfierkolben of same equipment, as in example 1, 550g 3.5% interlaced chlormethyliertes Styren of Divinylbenzen divinylbenzen-Kopolymeres with a chlorine value of 18,3% are registered and shifted with 1 650g Dichlorethan and agitated 2h at ambient temperature. Afterwards 200ml tin tetrachloride are proportioned and one with each with 40, 50, 60,70°C and 15h with 83-85 is agitated °C. The reaction product is separated and washed with methanol, methanol water 50:50 and water.

The product was analyzed, as follows,:

Surface: 1,361 m²/g

Water content: 41,9%

Surface for each unit volume of damp adsorbents: 573m²/ml.

A adsorbent-polymer manufactured after this example was washed to hot water with acetone and 60°C and submitted to a medicine adsorption test. A comparison with other with the Haemoperfusion assigned Adsorbentien shows the following composition:

Table 1: Medicine adsorption after 2h time of contact

type of adsorbent	imipramine (mg/ml)	Talinolol (mg/ml)	atropine sulfate (mg/ml)	Gluthalimid DIN (mg/ml)	Dihydropyri (mg/ml)
emoresin	10,3	9,4	7,1	8,4	7,8
WofatitUH91	9,3	3,8	4,1	11,9	6,6
of example (according to invention)	12,9	9,05	11,0	12,7	12,2